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EXAMINER	
JONES, DAMERON LEVEST	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/069,691	GILL ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Board Decision mailed 8/27/2009.

/D. Jones/ 1/5/11
Primary Examiner
Art Unit 1618

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of the amendment filed 8/9/10 wherein claims 6 and 8 were amended.

Note: Claims 1-14 are pending.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/19/10 has been entered.

RESPONSE TO APPLICANT'S ARGUMENTS/AMENDMENT

3. The Applicant's arguments and/or amendment filed 8/9/10 to the rejection of claims 1-14 made by the Examiner under 35 USC 103 and/or 112 have been fully considered and deemed persuasive-in-part for the reasons set forth below.

New Matter Rejection

The new matter rejection is WITHDRAWN because Applicant has amended the claims to overcome the rejections.

103 Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rajopadhye et al (US Patent No. 5,888,970) in view of Yamaguchi et al (JP 11-99192) in further view of Schott Glaswerke (DE 29,609,958) or Walther et al (US Patent No. 6,200,658).

It is noted that Board of Patent Appeals and Interferences decision on 8/27/09 concluded that secondary references (Yamaguchi et al, Schott Glaswerke, and Walther et al) establish that a diagnostic composition (i.e., a radiopharmaceutical) in a container which has a silica coating on the inner surface is obvious in the art (for a detailed

explanation of the secondary references and the Board of Patent Appeals and Interferences decision, Applicant is respectfully requested to review the office action mailed 8/27/09). Thus, in an attempt to overcome the prior art, the claims were previously amended to include the limitation that L is a carbon-containing chelating agent which comprises 2-6 or 8 heteroatoms selected from N, O, S, P, or Se.

Rajopadhye et al disclose labeled chelators that are incorporated into cyclic peptides that are useful as imaging agents (see entire document, especially, abstract; column 15, lines 9-24). In particular, the chelators may contain 2-10 heteroatoms selected from N, S, and O (column 3, lines 1-23). Possible chelators having various combinations of nitrogen, sulfur, and oxygen heteroatoms are disclosed in column 10 (lines 1-65), column 11 (lines 1-45), column 12 (lines 10-65), column 13 (lines 1-65), column 14 (lines 1-15); column 25 (lines 26-45), column 27 (lines 6-24), and column 28 (lines 16-60). The complexes may include radionuclides such as 99mTc and 111In (column 11, lines 55-59; columns 14-15, bridging paragraph). In addition, Rajopadhye et al disclose kits that may include the radiopharmaceuticals. The kits may contain one or more vials and all or part of the formulation may independently be in the form of a sterile solution or a lyophilized solid (column 16, lines 12-44). The kit may also contain solubilization aids such as butyl paraben (column 16, lines 52-59; column 30, lines 22-26). In addition, the kits may comprise a bacteriostat to inhibit the growth of bacteria in the kit during storage or before or after the kit is used to synthesize the radiopharmaceutical. Thus, while Rajopadhye et al disclose a radiopharmaceutical comprising a complex with an organic ligand which is carbon-containing chelating agent

comprising 2, 3, 4, 5, 6, and 8 heteroatoms selected from N, O, and S, a metal, and a kit which may comprise one or more vials and a bacteriostat, the reference fails to disclose that the container (e.g., vial) is silica coating on the inner surface. In addition, the reference fails to state that possible heteroatoms useful with their chelators include P and Se.

Yamaguchi et al disclose containers for radiopharmaceuticals and radiopharmaceutical preparations using the container. The objective of Yamaguchi et al was to develop containers for pharmaceutics which can prevent highly adsorbable radiopharmaceuticals from being adsorbed thereon and provide a clear description of their contents and the amounts thereof (see entire document, especially, page 1; page 3, 'Detailed Description of the Invention'; page 6, paragraph [0008]; page 7, paragraph [0011]). Yamaguchi et al solved the problem by coating the interior surface of a glass container with silica that is used to house radiopharmaceuticals (page 2, entire page; and page 3, claim 4). In claim 5, Yamaguchi et al invention is directed to a radiopharmaceutical preparation which is characterized in that a radiopharmaceutical container (the container is glass) has an interior surface that is coated with silica and filled with an adsorbable radioactive material (page 3, claim 5). Also, it is disclosed in the prior art, radioactive materials are used as tracers for diagnostic imaging in medical fields and that in some instances, a single element is used as the radioactive material and in other instances, label compounds are used which have specific in vivo behavior (page 4, paragraph [0002]. In addition, it is disclosed that detailed method of coating the interior surface of a glass container with silica are known in the art and are

commercially available under the name of Silicoat (the containers are made by Fuji Glass Corp.) (pages 7-8, bridging paragraph). It should be noted that while Yamaguchi et al discloses the use of thallium chloride as the radioactive material, the reference teachings are not limited to thallium chloride.

Walther et al disclose numerous applications for hollow glass bodies made from low melting glass material which requires an increase in the chemical resistance of the interior surface of the glass body. In order to avoid a disadvantageous dealkalizing process, the interior surface of the hollow glass body is coated. The interior surface may be coated with SiO2 (silicon dioxide, commonly known as silica) having a predetermined coating thickness according to the required chemical resistance or working conditions for forming the glass body. The coating is advantageously provided by means of a plasma chemical vapor deposition (PCVD) process (see entire document, especially, abstract; column 4, lines 39-44; and columns 4-5, bridging paragraph)

Schott Glaswerke discloses glass containers useful for storing pharmaceuticals and diagnostic solutions (see entire document, especially, page 1, first paragraph). One of the objects of Schott Glaswerke was to find a glass container for storing pharmaceutical or diagnostic solutions that remain largely inert with respect to the solutions (e.g., it was the desire of Schott Glaswerke to minimize the quantities of ions that leach out of the glass when storing the pharmaceutical or diagnostic solutions) (page 2, second complete paragraph). The problem of leaching of ions out of the glass was solved by coating the interior surface of the glass container with a layer of SiO2

(page 2, fourth complete paragraph; page 3, first paragraph). The layer may be generated by means of plasma chemical vapor deposition (PCVD) (page 2, fourth, fifth, and sixth complete paragraphs). In addition, Schott Glaswerke disclose that the composition of the glass of which the container is made is not critical, so long as the interior is coated with SiO2 (page 3, second, third, and fifth paragraphs; and page 4, 'Comparison' table and first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Rajopadhye et al using the teachings of Yamaguchi et al, Schott Glaswerke, and Walther et al to coat the inner surface of a container that has a radiopharmaceutical (the radiopharmaceutical comprises a coordination complex of a metal and an organic ligand) with silica for the reasons below. (1) Yamaguchi et al, Schott Glaswerke, and Walther et al all disclose various advantages of using glass vials that are coated with silica. (2) Both Yamaguchi et al and Schott Glaswerke disclose advantages of using glass with silica coated interiors for use with diagnostic compositions (i.e., radiopharmaceuticals). (3) A skilled artisan would have been motivated to use a silica coated glass interior in the invention of Rajopadhye et al in order to take advantage of one or all the advantages known in the art to be associated with silica coated interiors (i.e., avoid leaching of ions, provide a clear description of the container contents and the amounts thereof, etc.). (4) Also, a skilled artisan in the art would be motivated to use PCVD to coat the interior surface with silica because Schott Glaswerke and Walther et al disclose that it is well known in the art to use plasma chemical vapor deposition for coating glass surfaces with silica

and the advantages of the process. In particular, Schott Glaswerke and Walther et al disclose that glass containers coated with PCVD are significantly more resistant to leaching. (4) Furthermore, it would also be obvious to generate a kit comprising the radiopharmaceutical metal complex wherein the metal complexes may include P and Se because a skilled artisan would not only recognize that all the heteroatoms (N, O, S, P, and Se) of interest in the instant invention are non-metals from Groups VA and VIA, but would recognize that the replacement of one equivalent with another from the same Group would not drastically alter the overall properties of the contrast agent.

Since Rajopadhye et al, Yamaguchi et al, and Schott Glaswerke are all directed to diagnostic compositions (i.e., radiopharmaceuticals), the references may be considered to be within the same field of endeavor. Thus, the reference teachings are combinable. Furthermore, since, Schott Glaswerke, Yamaguchi et al, and Walther et al all are directed to silica coated glass interiors, the references may be considered to be within the same field of endeavor. Hence, those reference teachings are combinable.

APPLICANT'S ASSERTIONS

In summary, Applicant makes the following assertions. (1) It would have not been obvious to one of ordinary skill in the art that the motivation to combine Rajopadhye and Yamaguchi stems from the advantages taught by Yamaguchi. Specifically, Applicant refers to the passage in Yamaguchi that contains the phase "...prevent highly adsorbable radiopharmaceutical from being adsorbed thereon and provide a clear description of the vial contents and amounts thereof…". Applicant further asserts that in Yamaguchi (paragraphs [0005], [0010], [0011], and [0016] –

[0019]) it is clear that the advantages of the content's description is provided by reversed text lettering on the outside of the vial, not the silica coating. Applicant's position is that the silica coating feature is completely different in Yamaguchi and would have motivated one to generate an invention that is outside the scope of the instant invention. Specifically, Applicant asserted that the combination of references would lead to radiopharmaceutical vials having the reversed lettering of Yamaguchi, not the silica coating.

(2) Secondly, Applicant asserts that the clear teaching of Yamaguchi itself is that the invention therein is useful for highly adsorbable radiopharmaceutical while the Rajopadhye reference does not teach or suggest that their radiopharmaceuticals is suffering from any adsorption problems. Hence, Applicant has concluded that there is no motivation to combine Rajopadhye and Yamaguchi as suggested by the Examiner since the radiopharmaceutical of Rajopadhye do not fit the criterion taught in Yamaguchi. Thus, Applicant has concluded that the combination of Rajopadhye and Yamaguchi is believed to be invalid.

(3) Next, Applicant asserts that the Examiner's motivation to combine Rajopadhye and Schott Glaswerke stems from the advantages taught by Schott Glaswerke for radiopharmaceuticals. Applicant is requesting that the examiner specifically disclose where in Schott Glaswerke any reference to radioisotopes and/or radiopharmaceuticals may be found. Applicant's position is that Schott Glaswerke is silent on radiopharmaceuticals. Furthermore, Applicant asserts that whether or not

Schott Glaswerke disclose radiopharmaceuticals is crucial to the examination of the instant application.

(4) Then, Applicant asserts that Schott Glaswerke references only the storage of pharmaceutical or diagnostic solutions and blood and blood samples. Thus, Schott Glaswerke read without hindsight is silent on radioisotopes and formulations thereof used in medicine.

(5) Finally, Applicant asserts that Rajopadhye and Schott Glaswerke were not properly combined since they are from different fields of endeavor. Applicant refers to Walther which the Examiner relies on as an alternative to Schott Glaswerke. As evidence of Applicant's position, Applicant compares the classification codes for Rajopadhye and Walther stating that no subject codes are common for the documents.

EXAMINER'S RESPONSE

First, it is noted that Applicant has repeatedly presented the argument that the combination of references would not have resulted in one of ordinary skill using a silica coating. Applicant appealed the Examiner's position to the Board of Patent Appeals and Interferences to resolve this issue. The Board resolved this issue in their decision mailed to Applicant on 8/27/09. A copy of the decision is attached to this office action. However, since Applicant is not in agreement with the Board's decision, Applicant continues to argue that the coating is not obvious in the hopes that the Examiner will disagree with the Board's decision and the Examiners' positions taken during the prosecution of this application. But, it is the Examiner's position that whether or not the silica coating is obvious based on the cited prior art was resolved by the Board. The

Examiner is in agreement with the Board's decision and thus, based on the prior art cited one would be motivated to use a silica coating. It is believed that no further arguments are necessary on an issue that was resolved by the Board.

In regards to Applicant's assertion that there is no motivation to combine Rajopadhye and Yamaguchi, it is noted that both documents disclose applications that are applicable to radiopharmaceuticals. Thus, just because Yamaguchi focuses on containers for radiopharmaceuticals should not be interpreted as the radiopharmaceuticals of Rajopadhye are not the same as that of Yamaguchi. In both instances, the references are using radiopharmaceuticals and placing those radiopharmaceuticals into a container (i.e., vial).

In regards to Applicant assertions that Rajopadhye and Schott Glaswerke were not properly combine and request for the Examiner to disclose any possible reference to a radioisotope and/or radiopharmaceutical in Schott Glaswerke, the following response is set forth. Both documents are directed to pharmaceutical/diagnostic solutions. Pharmaceuticals are used for various diagnostic purposes including radiopharmaceutical purposes. For evidence of the Examiner's position, Applicant's attention is directed to Rajopadhye (see abstract) which discloses that the radiolabeled compounds may be used for diagnosing thrombi. Also, Applicant is respectfully requested to review column 1, lines 10-16; column 2, lines 16-21; and column 16, lines 12-22, of Rajopadhye for evidence of the use of the radiopharmaceutical for diagnostic purposes. In addition, Rajopadhye disclose that the compositions which are initially non-radiolabeled are radiolabeled with a radionuclide (see column 2, lines 41-61;

column 11, lines 55-61; column 12, lines 1-61; column 13, lines 1-61; columns 14-15, bridging paragraph; column 15, lines 9-35). Hence, the skilled artisan would recognize that a diagnostic pharmaceutical would include radiopharmaceuticals and if both Rajopadhye and Schott Glaswerke disclose diagnostic compositions, and Rajopadhye specifically refers to their diagnostic pharmaceutical as a radiopharmaceutical, then Schott Glaswerke's reference to 'pharmaceuticals and diagnostic solutions' would include non-radiolabeled pharmaceutical and diagnostic (i.e., radiolabeled) pharmaceuticals. Hence, the combination of references would be obvious to a skilled artisan.

In regards to Applicant's assertion that the references were not properly combined, it should be noted that while Rajopadhye disclose a radiopharmaceutical comprising an organic ligand as claimed by Applicant, a metal, and a kit that may comprise one or more vials and a bacteriostat, the reference failed to disclose that the vial is coated with silica. Yamaguchi et al was cited for its teachings in the art regarding containers for radiopharmaceuticals. Walther was cited for its teachings on the interior surface of containers and why one would want to use a silica coated container. Schott Glaswerke was cited for its teachings on containers for storing pharmaceutical and diagnostic solutions. All of the references in involved a container. Rajopadhye, Schott Glaswerke, and Yamaguchi involve pharmaceutical and diagnostic compositions. Schott Glaswerke and Walther disclosed silica containing containers. Thus, Applicant is reminded that the secondary references do not have to disclose each limitation of the claim. The purpose of those documents is to illustrate teachings known in the art and

provide motivation as to why one would desire a silica coated container for the radiopharmaceutical.

In the Board's decision, many of the issues of the issues set forth in Applicant's response filed 8/19/10 were resolved (see the next few paragraphs below). The only modification to the Board's decision is the reference to Crane instead of Rajopadhye. However, it should be noted that the Rajopadhye document replaced Crane because Applicant amended the claims to and organic ligand having a particular formula which was not taught by Crane, but is present in Rajopadhye. But, both Crane and Rajopadhye disclose a radiopharmaceutical comprising an organic ligand, metal and kit having one or more vials and a bacteriostat.

STATEMENT OF THE CASE

Claims 1-14 are pending and on appeal (App. Br. 1).[2] Claims 1, 6, 10 and 11, the independent claims, are representative and read as follows:

1. In a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, the improvement being that the radiopharmaceutical comprises a coordination complex of a metal with an organic ligand.

6. A kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.

10. A composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises (i) a stabilizer capable of stabilizing said radiopharmaceutical metal complex; and (ii) an organic ligand which forms a coordination complex with the metal; in a container which has a silica coating on the inner surface.

11. A composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

The Examiner cites the following documents as evidence of unpatentability:

Crane et al.	US 5,961,952	Oct. 5, 1999
Walther et al.	US 6,200,658 B1	Mar. 13, 2001
Schott Glaswerke (as translated)	DE 29,609,958 U	Oct. 2, 1996
Yamaguchi et al.	JP 11-99192	Apr. 13, 1999

(as translated)

The Examiner has rejected claims 1-14 under 35 U.S.C. § 103(a) as being unpatentable over Crane and Yamaguchi in view of Schott Glaswerke or Walther (Ans. 4-8).[3]

OBVIOUSNESS

ISSUE

The Examiner cites Crane as disclosing "a radiopharmaceutical comprising a complex with an organic ligand and metal and a kit which may comprise one or more vials and a bacteriostat" (Ans. 4-5). The Examiner concedes that Crane "fails to disclose that the container (e.g., vial) [has a] silica coating on the inner surface" (*id.* at 5).

To meet that limitation, the Examiner cites Yamaguchi as disclosing "containers for pharmaceutics which can prevent highly adsorbable radiopharmaceuticals from being adsorbed thereon," the containers having "an interior surface that is coated with silica" (*id.*). The Examiner also cites Walther as disclosing the use of silica coatings on the inner surfaces of hollow glass bodies "to avoid a disadvantageous dealkalizing process" (*id.* at 6). The Examiner further cites Schott Glaswerke as disclosing a glass container for storing pharmaceutical or diagnostic solutions in which the "problem of leaching of ions out of the glass was solved by coating the interior surface of the glass container with a layer of an SiO2" (*id.*).

Based on these teachings, the Examiner finds that a "skilled artisan would have been motivated to use a silica coated glass interior in the invention of Crane et al in order to take advantage of one or all [of] the advantages known in the art to be associated with silica coated interiors" (*id.* at 7).

Appellants contend that the Examiner failed to make a prima facie case of obviousness because the cited references do not teach or suggest all of the limitations in the rejected claims, and because the references do not provide motivation for combining them with each other (App. Br. 4). Specifically, Appellants assert that Crane contains only a passing reference to the vials containing its radiopharmaceutical metal complexes, and the remaining references do not disclose that their silica-coated containers can be used with radiopharmaceutical metal complexes (*id.* at 5; *see also* Reply Br. 5 (urging that Schott Glaswerke's disclosure does not relate to radiopharmaceuticals)).

Moreover, Appellants argue, Yamaguchi solves the problem of adsorption of ionic radiopharmaceuticals to the containers' inner surfaces, as opposed to complexed metals, and therefore would not have prompted an ordinary artisan to modify the inner surface of Crane's metal complex-containing vials (App. Br. 6; *see also* Reply Br. 6). Also, Appellants argue, given the many coatings capable of being used, the many features in Crane capable of variation or improvement, and the fact that Crane gives little consideration to the properties of its vials much less their inner surfaces, the Examiner's conclusion that it would be obvious to apply the specifically claimed coating to the inner surface of Crane's vials amounts to impermissible hindsight (App. Br. 7-9; *see also* Reply Br. 3-4 (pointing out that Walther and Schott Glaswerke disclose a number of coatings in addition to silica)).

Appellants further argue that, given Crane's disclosure of the use of a solubilization aid for its radiopharmaceutical metal complexes, an ordinary artisan would not have been prompted by Yamaguchi to put a silica coating on the inner surface of Crane's containers, "in that the absence of the 'solubilization aid' would remove an essential teaching of Crane. Accordingly, combining Crane and [Yamaguchi] in this manner is an invalid combination" (App. Br. 10; *see also* Reply Br. 9).

Appellants further argue that the references teach away from the claimed combination of features because an ordinary artisan, "even if assumed to be contemplating improvements of Crane, would focus on the specific teachings in Crane of embodiments taught to be important, and be motivated to improve those elements" rather than the barely mentioned vial (App. Br. 11). Moreover, Appellants urge, the "present invention is a selection invention where unexpected advantages for radiopharmaceuticals that are metal complexes of ligands have been found. The novelty lies in the selection, where the claimed subject matter has unforeseen advantages" (Reply Br. 7; *see also id.* at 8-9).

In view of the positions advanced by Appellants and the Examiner, the issue with respect to this rejection is whether Appellants have shown that the Examiner erred in concluding that an ordinary artisan would have considered it obvious to provide the inner surfaces of Crane's radiopharmaceutical metal complex-containing vials with a silica coating as taught in Yamaguchi, Walther, and Schott Glaswerke.

BOARD OF APPEAL FINDING OF FACTS ('FF')

8. Yamaguchi discloses "a container for radiopharmaceuticals characterised in that the interior surface of a glass container is coated with silica" (Yamaguchi [0011]).

9. Yamaguchi discloses:

> [T]he silica film coated on the interior surface of the glass container plays a role in preventing the pharmaceutical solution from coming into contact with water-soluble components such as alkalis included in the glass. That is to say, alkali components such as sodium ions (Na^+) and potassium ions (K^+) are present in the glass, and these components might be dissolved by the pharmaceutical solution. It is believed that in this solution state there is an equilibrium between the potassium ions and the glass; a constant amount of potassium ions is always present in solution, but potassium ions themselves change their state back and forth between the free state and the state in which they are bonded to the glass.

(*Id.* at [0013].)

10. Yamaguchi explains:

> When using an aqueous solution containing radioactive thallium chloride (^{201}Tl) as the radiopharmaceutical, since the thallium is present as a monovalent cation and not as a trivalent cation, it can be expected to show the same properties as those of potassium, which is a monovalent cation. Since the thallium ions show the same properties as those of potassium ions, the potassium ions and thallium ions react with the glass competitively. As a result, a constant amount of thallium is always adsorbed on the glass. Therefore, even if a precise amount of the radiopharmaceutical is administered to a patient, it is short by an amount corresponding to the amount of adsorbed thallium and the required amount of the radiopharmaceutical cannot be administered to the patient correctly.

(*Id.* at [0014].)

11. Yamaguchi discloses that "[w]hen the interior surface of the glass container is coated with silica, the dissolution of potassium from the glass can be suppressed, and thus the equilibrium reaction between thallium and potassium is not caused so preventing thallium from being adsorbed thereon" (*id.* at [0015]).

12. Walther discloses that "[l]ow melting glass materials, such as borosilicate glasses or calcium, sodium glasses, corrode in a known manner on contact with water or other liquids. Particularly water withdraws sodium ions from glass" (Walther, col. 1, ll. 19-22).

13. In view of the problem of ions leaching from glass, Walther discloses that "[h]ollow glass bodies, which require an increased chemical resistance for the interior surface, are, for example, those used . . . for components used for biotechnology reactors, and as containers for medicinal purposes (e.g. ampoules, bottles, injector devices, cylindrical ampoules, etc.). The latter mentioned applications are of special significance" (*id.* at col. 1, ll. 27-43).

14. To address the problem of ions leaching from glass Walther discloses "a glass tube made from low melting glass material and acting as a semifinished product for forming a hollow glass body with an interior coating having a high chemical resistance or inertness" (*id.* at col. 1, ll. 13-16).

15. Walther discloses that, for coating the inner surfaces of its tubes, "the following oxides may be used, among others . . . : SiO_2, Al_2O_3, TiO_2 or mixtures thereof" (*id.* at col. 4, ll. 40-42).

16. Walther discloses:

> Because of the invention it is also possible to prepare glass tubes with increased interior chemical resistance so that the predominant part of the surface of the entire system is provided with a high chemical resistance after a possible shaping process, while a comparatively smaller area portion is left with a lesser chemical resistance. Exemplary applications include: glass tubes which are used in biotechnology and are used with media which is absorbed in standard glass surfaces, containers for medical purposes in which the total ion leach out from the container plays an important role, (e.g. for dispensing alkali and other metal ions).

(*Id.* at col. 3, l. 59, through col. 4, l. 2.)

17. Schott Glaswerke discloses that it is "known that with all glass containers, even glass containers that are made of borosilicate glass and which, according to the pharmacopeias (for example, Deutsches Arzneibuch DAB 10 [German Pharmacopoeia]) are classified in the high durability class, reactions of the glass surface with the solutions can be demonstrated" (Schott Glaswerke 1).[4]

Notes:

> [4] This document is not paginated. We therefore refer to the first page as page 1, and the remaining pages as if the document were paginated consecutively.

18. Schott discloses that the reaction between glass containers and the solutions inside them "is due primarily to the alkaline substances leaching from the glass surface and caused by the aqueous solution. This leaching during storage may result in an undesired increase in the pH[;] for example, if water for injection purposes is involved, it may [be] several pH units higher" (*id.* at 1-2).

19. To address the problem of ions leaching from glass, Schott discloses "a glass container for storing pharmaceutical or diagnostic solutions that remains largely inert with respect to these solutions, i.e., in which the quantities of ions that leach out of the glass as a result of these solutions is minimized" (*id.* at 2).

20. Schott discloses that the "glass container is coated on the inside, i.e., on the surface that is contact with the solutions, with a layer of oxides and/or nitrides of elements Si, Ti, Ta, Al or mixtures thereof, with the layer being produced by means of the plasma CVD method (PCVD method)" (*id.*).

21. Schott discloses that "[s]urprisingly, it was found that a glass container having coatings in accordance with the PCVD or PICVD method is significantly more resistant to leaching and, as a result, its behavior relative the solutions stored in it is significantly more inert" (*id.*).

22. Schott further discloses that "[e]specially suitable are oxidic layers, more particularly layers made of SiO_2 and TiO_2, with SiO_2 being preferred" (*id.* at 3).

PRINCIPLES OF LAW

As the Supreme Court pointed out in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Rather, the Court stated:

> [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419 (emphasis added); *see also id.* at 418 (requiring a determination of "whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue") (emphasis added).

While it recognized the importance of providing a rationale for practicing the claimed subject matter, the Court also reaffirmed that "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). The Court reasoned that:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable
>
> solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Id. at 421.

The Court also noted that the analysis under 35 U.S.C. § 103 properly "take[s] account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418; *see also id.* at 421 ("A person of ordinary skill is . . . a person of ordinary creativity, not an automaton.").

The Court further noted that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it." *Id.* at 421 (citations omitted.)

It is well settled that evidence of unexpected results may rebut an examiner's prima facie case of obviousness. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998); *see also KSR*, 550 U.S. at 416 ("The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art") (discussing *United States v. Adams*, 383 U.S. 39 (1966)).

However, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

ANALYSIS

Appellants' arguments do not persuade us that the Examiner's conclusion of obviousness is erroneous.

Claim 1 recites a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, "the improvement being that the radiopharmaceutical comprises a coordination complex of a metal with an organic ligand." Crane discloses a solution containing the radiopharmaceutical metal-ligand complex ^{99m}Tc-TBI in a vial (FF 5). The solution is for administration to a patient to allow imaging of breast cancer tumors (FF 1).

Thus, Crane differs from claim 1 only in that Crane does not disclose that the vial has a silica coating on its inner surface. However, each of Yamaguchi (preventing adherence of radiopharmaceuticals to containers' inner surfaces (FF 8-11)), Walther (preventing ions from leaching from glass containers into medically administered solutions (FF 12-16)), and Schott (ion leaching/pH change prevention in medical solutions (FF 17-21)), discloses that it is advantageous to provide a silica coating to the inner surfaces of containers that hold medical solutions. We therefore agree with the Examiner that an ordinary artisan following the teachings of Crane, advised by the other references of the advantages of a silica inner coating on containers having the same purpose as Crane's, would have been prompted to place a silica inner coating on Crane's containers.

We acknowledge that, other than containing the radiopharmaceutical solutions, Crane discloses little about the properties of its vials. However, that fact does not render claim 1 any less obvious, given the advantages of silica inner coatings disclosed by the other references. It is well settled that

it is legal error to evaluate a claim's obviousness by using blinders to focus on a single reference while ignoring relevant teachings in other references. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.").

We acknowledge Yamaguchi's disclosure that its inner coating prevents adsorption of ionic, rather than complexed, radiopharmaceuticals (*see* FF 9-11). We also acknowledge Crane's disclosure of the importance of a solubilization aid in its radiopharmaceutical formulations (*see* FF 2, 3, 6). However, given Walther's and Schott's disclosures of the desirability of rendering inert the inner surfaces of containers of medically administered solutions (FF 13, 16, 18, 19), we cannot agree that an ordinary artisan lacked the impetus to give Crane's vials a silica inner coating.

Moreover, while Appellants aver that the claimed coating provides unexpected results, Appellants point to no comparison between the closest prior art and an embodiment encompassed by the claims. It is well settled that argument by counsel is no substitute for actual evidence. *In re Cole*, 326 F.2d 769, 773 (CCPA 1964); *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

In sum, we are not persuaded that the Examiner erred in concluding that an ordinary artisan would have considered it obvious to provide the inner surfaces of Crane's radiopharmaceutical metal complex-containing vials with a silica coating as taught in Yamaguchi, Walther, and Schott Glaswerke. We therefore affirm the Examiner's rejection of claim 1 as being obvious over those references. Claims 2-5 were not argued separately and therefore fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Claim 6 recites "[a] kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface." As noted above, Crane discloses a kit comprised of a vial that contains the non-radioactive organic ligand tertiary butyl isonitrile, which can be lyophilized or in solution (FF 4).

Thus, Crane differs from claim 6 only in the lack of a silica coating on the container's inner surface. For the reasons discussed above, we agree with the Examiner that an ordinary artisan would have considered such a coating obvious. We therefore also affirm the Examiner's obviousness rejection of claim 6, and its dependent claims 7-9, which were not argued separately.

Claim 10 recites "[a] composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises (i) a stabilizer capable of stabilizing said radiopharmaceutical metal complex; and (ii) an organic ligand which forms a coordination complex with the metal; in a container which has a silica coating on the inner surface." As noted above, in addition to solubilization aids, buffers, and bacteriostats, any of which can be considered stabilizers, Crane's metal complex-containing solutions may also include "stabilization aids" (*see* FF 3).

Thus, Crane differs from claim 10 only in the lack of a silica coating on the container's inner surface. As discussed above, we agree with the Examiner that an ordinary artisan would have considered such a coating

obvious. We therefore also affirm the Examiner's obviousness rejection of claim 10, and its dependent claims, which were not argued separately.

Claim 11 recites "[a] composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface." As noted above, Crane includes a bacteriostat in its compositions (FF 3), and therefore differs from claim 11 only in the lack of a silica coating on the container's inner surface.

As discussed above, we agree that an ordinary artisan would have considered such a coating obvious, and therefore affirm the Examiner's obviousness rejection of claim 11, and its dependent claims, which were not argued separately.

In sum, we affirm the Examiner's rejection of claims 1-14 under 35 U.S.C. § 103(a) as being unpatentable over Crane and Yamaguchi in view of Schott Glaswerke or Walther.

In conclusion, based on the cited prior art and the Board's decision, the rejection is deemed proper.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (571)272-0617. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D. L. Jones/
Primary Examiner
Art Unit 1618

January 5, 2011